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PATREA L PABST
ARNOALL GOLDEN & GREGORY LLP
2800 ONE ATLANTIC CENTER
1201 WEST PEACHTREET STREET
ATLANTA GA 30309-3450

| EXAMINER | |
|---|---|
| BAKER, A | |
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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Paper No. 28

Application Number: 08/965,356
Filing Date: 11/16/97
Appellant(s): Bernfield et al.

Patrea L. Pabst
For Appellant

# EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed .

## *(1) Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

## *(2) Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

*(3) Status of Claims*

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 1, 3-5, 10, and 12-14.

Claims 6 and 15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Appellant's have omitted Claim 12 under "Status of Claims on Appeal" and in the Appendix of Pending Claims. Claim 12 also was not included in the Grouping of Claims. However, it was included under the section on Issues on Appeal.

Claim 12 reads as follows:

**12. The method of claim 10 wherein the syndecan is syndecan-1.**

*(4) Status of Amendments After Final*

The Appellants' statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 10/27/99 has not been entered.

Appellants are correct in stating that the claims were last amended by the amendment filed January 7, 2000

*(5) Summary of Invention*

The summary of invention contained in the brief is correct.

*(6) Issues*

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Claim 10 is also pending and on appeal, having been rejected under 35 U.S.C. § 112, first paragraph. Thus, Claims 1, 3-5, 10, and 12-14 stand rejected under 35 U.S.C. § 112, first paragraph.

*(7) Grouping of Claims*

Claim 12 is not included in the Grouping of Claims. According to Applicants' grouping, Claim 12 would have fallen into the second group, covering the method claims.

Appellant's brief includes a statement that the claims do not stand or fall together. Two groups are suggested. However, no reasons in support thereof are included. Under 37 CFR 1.192(c)(7) Appellant is required to explain why the claims of the group are believed to be separately patentable. Merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable.

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the transgenic rodents of Appellant's Group I are required to carry out the methods of Appellant's Group II. Since the methods cannot be carried out without the

transgenic rodents, the claims stand and fall together. Furthermore, the basis for the rejection of all claims in both groups is the same. Thus, all claims stand and fall together.

*(8) Claims Appealed*

Claims 1, 3-5, 10, and 12-14 are pending and on appeal. A listing of the claims on appeal appear in the Appendix to the Appellant's brief. However, Claim 12 was omitted. Claim 12 reads as follows:

**12. The method of claim 10 wherein the syndecan is syndecan-1.**

*(9) Prior Art of Record*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

**Hammer et al.** (1990) Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human b2m: An animal model of HLA-B27-associated human disorders. Cell, Vol. 63, pp. 1099-1112.

**Mullins et al.** (1990) Fulminant hypertension in transgenic rats harbouring the mouse Ren-2 gene. Nature, Vol. 344, pp. 541-544.

**Mullins et al.** (1989) Expression of the DBA/2J Ren-2 gene in the adrenal gland of transgenic mice. EMBO J., Vol. 8, No. 13, pp. 4065-4072.

**Taurog et al.** (1988) HLA-B27 in inbred and non-inbred transgenic mice. J. Immunol., Vol. 141, No. 11, pp. 4020-4023.

**Wall, RJ** (1996) Transgenic livestock: Progress and prospects for the future. Theriogenology, Vol. 45, pp. 57-68.

***(10) Grounds of Rejection***

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 3-5, 10, and 12-14 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse having a genome comprising a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, wherein expression of the DNA sequence results in the mouse developing maturity onset obesity and methods of using said mice, does not reasonably provide enablement for any transgenic rodent expressing a syndecan from a transgene construct. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1 and 3-5 are drawn to a transgenic rodent whose genome comprises a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, wherein expression of the DNA sequence results in the rodent developing maturity onset obesity. Claims 10 and 12-14 are drawn to methods for screening for compounds which can alter body weight.

The specification fails to provide an enabling disclosure for the preparation and use of any transgenic rodent having a syndecan gene integrated into the genome such that syndecan is expressed from a heterologous construct, because no guidance is provided in the specification fro the preparation and use of any transgenic rodent other than mice. The claims encompass any rodent having a syndecan transgene, but the specification is enabling only for mice. As discussed herein below and in the previous Office Actions (Paper Nos. 8 and 13), phenotypic alterations resulting from the introduction of a transgene into an animal's genome cannot be predicted, even when the function of the gene is known. Thus the model system of Claims 10-15, wherein the transgenic rodents are useful for the screening of compounds which can alter body weight is enabled only for transgenic mice expressing a syndecan transgene of the type disclosed in the specification. The phenotype of any other transgenic rodent expressing an exogenous syndecan cannot be predicted and has not been demonstrated.

The specification fails to provide an enabling disclosure for the preparation of any species of transgenic rodent of the type claimed because the phenotype of a transgenic animal cannot be predicted. In the absence of a transgene-dependent phenotype, one skilled in the art would not know how to use the claimed animals. The phenotype of any species of rodent expressing a syndecan-encoding transgene as recited in the claims, cannot be predicted. The specification does not teach what phenotype would be observed in any species of transgenic rodent of the type claimed other than the mouse. Furthermore, the specification does not adequately teach how one would have prepared any and all transgenic rodents expressing a

syndecan-encoding transgene, because the specification does not teach constructs with appropriate regulatory regions that would work in any rodent, thereby imparting an obese phenotype to the resultant transgenic animal. The mere capability to perform gene transfer in any given species is not enabling for the claimed transgenic rodents because a predictable phenotype cannot be achieved by simply introducing a transgene encoding a gene of interest. While gene transfer techniques are well-developed for a number of species, especially in the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse will not necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design

transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, there are inherent physiological differences between mice, rats, and other rodents that can affect the phenotype in an unpredictable manner. In the absence of representative working examples, the existence of any phenotypic alteration resulting from the introduction of a syndecan-encoding transgene in any rodent species, is highly unpredictable. Without knowing the phenotype of the transgenic rodent, one of skill in the art would not know how to use the animal. Given the lack of working examples, the limited guidance in the specification, and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the full scope of the claimed transgenic rodents.

While the species-specific requirements for transgene design are not clearly understood, examples in the literature demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al., 1990 produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human $b_2$-microglobulin

transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover any species of transgenic rodent having a syndecan-encoding transgene, but the specification does not enable the full scope of the claimed animals. In the absence of disclosure of transgenic rodents, exhibiting a transgene-dependent phenotype, representative of the full scope of the claimed transgenic animals, undue experimentation would have been required to make and use the claimed animals.

The specification fails to provide an enabling disclosure for the preparation of any transgenic rodents carrying a syndecan-encoding transgene construct other than mice. The specification describes the preparation of mice expressing a transgene construct comprising a nucleic acid molecule encoding syndecan-1 operably linked to the CMV promoter/enhancer regulatory regions, wherein expression of the transgene results in mice that exhibit maturity onset obesity. Syndecans have been identified in the mouse, rat, hamster, and human. However, other animals for which syndecans have not been identified, or for which the gene for a syndecan is not known, are not enabled for the generation of transgenics that overexpress

a syndecan transgene. Furthermore, phenotypic alterations resulting from the introduction of transgenes is highly unpredictable. Given the lack of any demonstration of a maturity onset obesity resulting from expression of a syndecan transgene in any rodent other than the mouse and given the unpredictability of obtaining a specific phenotypic alteration as the result of the introduction of a defined transgene construct, one skilled in the art would have been required to have exercised undue experimentation to have practiced the invention in any animal other than the mouse. Thus, limitation to mice carrying the claimed transgene construct is appropriate.

*(11) Response to Argument*

Appellants argue that, in the field of obesity and transgenics, mice and rats are interchangeable. The Examiner does not agree. Appellants refer to articles "that demonstrate that results obtained with mice are predictive of results obtained with rats." However, the "results" that Appellants refer to are not results obtained using **transgenic** mice and rats. Rather, these references describe either natural mutations or surgical lesions that result in **loss-of-function**, and the effects of these mutations or lesions on the weight of the animal. With the exception of the growth hormone example, none of the references cited involve transgenesis and the **overexpression** of a transgene *in vivo*. Loss-of-function mutations are not analogous to overexpression methods. Loss-of-function mutations do not involve transgene expression (or the production of transgenic animals), an essential feature of the claimed invention. The instant invention involves transgenesis and **overexpression** of an endogenous gene (murine syndecan-1 in mouse). The level and location of transgene expression are crucial to the development of phenotype. Furthermore, the temporal pattern of expression is a critical determinant of phenotype. The Examiner has already cited four references [Mullins et al. (1989), Mullins et al. (1990), Taurog et al. (1988), and Hammer et al. (1990)] that demonstrate that when an identical transgene construct is used in both rats and mice, completely different phenotypes result in the two species, **even though** both express the transgene. The examples were summarized as follows at page 5 of the final rejection of 2/1/00:

> While the species-specific requirements for transgene design are not clearly understood, examples in the literature demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al., 1990 produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human $\beta_2$-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Appellants have pointed to these examples as successes because **expression** of the transgene was obtained in both rats and mice. On the contrary, the take-home lesson from these studies is that **even though** some level of expression is attained in both species, the phenotypes of the rats and mice are **completely different**. **Expression** is clearly **not sufficient** to produce the expected or desired phenotype. These examples show that, in the field of transgenics, studies in mice are **not predictive** of the same results in rats. The instant specification does not disclose the level of syndecan expression that would be required in a rat or other rodent to produce a phenotype of maturity onset obesity. Thus, the level of expression sufficient to produce the desired phenotype in a rat or other rodent is not known. Given the unpredictability in the art, undue experimentation would have been required for one skilled in the art to determine the level of expression required and to design appropriate transgene constructs that would produce the required level of product in the appropriate tissue. The level and location of transgene expression are crucial to the development of the phenotype. In the instant case, the skilled artisan would not know how to produce a level of expression sufficient

to produce the desired phenotype or even if the desired phenotype can be produced at any level of expression. The state of the art renders it unpredictable as to whether one skilled in the art could produce a transgenic rat or other rodent (with the exception of mice) expressing a sufficient amount of any syndecan to produce an obese phenotype. Thus, undue experimentation would have been required to produce the full scope of the claimed transgenic rodents.

Appellants' arguments are limited to the rat. However, the claims are directed to all rodents. There are **4,000 species** of rodents, including squirrels, chipmunks, porcupines, woodchucks, gophers, gerbils, chinchillas, etc. For the reasons stated above and in the final rejection of 2/1/00, the specification is not enabling over the full scope of **all rodents**.

On page 9 of the Brief, Appellants refer to studies for diabetic mice and rats, mice and rats with high fat induced hyperleptinemia, VMH lesioned mice and rats, and genetic defects resulting in obesity. As discussed above, none of these examples involve producing transgenic animals. Furthermore, it is noted that all references directed to rats are **post-filing art**. Post-filing art cannot be used to enable the instant invention. At the time of the invention, the skilled artisan did not have the benefit of the information relating to obesity in rats, and therefore could not have used this information in the development of appropriate transgene constructs and transgenic rats.

Appellants argue that an identical methodology is used to generate transgenic mice and rats. As noted on page 8, paragraph 3 of the final rejection of 2/1/00, the methodology for

producing transgenic rodents is not an issue in the rejection. The enablement rejection is predicated on the unpredictability of using transgenic technology to produce a defined phenotype in any and all rodent species. The **effect** of transgene expression (i.e. the phenotype) is unpredictable, as exemplified in the cited references. The mere capability to perform gene transfer in any given species is not enabling for the claimed transgenic rodents because a predictable phenotype cannot be achieved by simply introducing a transgene encoding a gene of interest. The cited examples aptly demonstrate that gene transfer and even gene expression are **not sufficient** to produce the same phenotype in mice and rats.

Appellants argue that identical phenotypes result from transgenic expression of heterologous genes in the hypothalamus of rats and mice, using a growth hormone (GH) transgene. Appellants state that when a human GH transgene is introduced into mice or rats in an unregulated manner, both species exhibit acromegaly, obesity and diabetes. Appellants argue that, given this example, the data from transgenic mice expressing the syndecan could be easily extrapolated to rats. However, growth hormone is not a syndecan and is not a related protein. Moreover, the data from these experiments were not available to the skilled artisan at the time of the invention, and so could not have been used as a guideline for the development of other transgenic species. Appellants cite Bartke et al. (1999) and Ikeda et al. (1998), both of which are **post-filing** art. Post-filing art cannot be used to supplement the specification to provide an enabling disclosure.

Appellants argue that the CMV promoter can be expected to produce the same expression pattern in rats as in mice because Wang et al. (1998) demonstrated that *in vivo* delivery of the kallikrein gene produced expression in the hypothalamic nuclei in rats and the instant specification demonstrates expression in the hypothalamus of mice. However, given that Wang et al. (1998) is post-filing art, the skilled artisan would not have been able to use this information as guidance when making transgene constructs because this data was not available at the time of the invention. Moreover, as discussed above, expression alone is not sufficient to produce a desired phenotype. Furthermore, the rats described by Wang et al. were not transgenic animals. Those experiments involved *in vivo* gene delivery to the third ventricle.

Appellants argue that the mechanisms of obesity in mice and rats are identical. Appellants state that the leptin receptor is the *ob* (obese) gene product. This is incorrect. The leptin receptor is the *db* gene product. Appellants state that mutations in the leptin receptor in both mice (*db/db*) and rats (Zucker *fatty*) cause early onset obesity in an identical physiological manner. However, as discussed above, these are **loss-of-function** mutations and loss-of-function mutations are not analogous to transgene **overexpression**. The production of transgenic animals and transgene overexpression are critical features of the claimed invention. The level and location of transgene expression must be sufficient to produce the desired phenotype.

Appellants argue that hypothalamic lesions give rise to identical obesity syndromes in mice and rats. Again, as discussed above, surgical lesions which result in the loss of function of cells in a particular region of the brain, fails to predict what will happen under conditions where overexpression is relied upon to produce an obesity phenotype. These experiments do not involve the production of transgenic animals, a critical element of the claimed invention, and therefore are not predictive of the effects of transgene overexpression in rats. Furthermore, two of the references relied upon, Flier et al. (1998) and Augustin et al. (1999) are post-filing art.

Appellants argue that the claims only encompass those animals possessing the claimed phenotype. Appellants state that the rejection appears to be premised on an allegation that animals not possessing the claimed phenotype fall within the claims. This is incorrect. The rejection relies upon the unpredictability for producing the phenotype recited in the claims, over the full scope of all rodents.

Appellants argue that the lack of evidence with rodents other than mice is not conclusive. Appellants suggest that the instant situation is analogous to the production of monoclonal antibodies, where only 2.3% of the hybridomas produced gave the claimed monoclonal antibody. The Examiner does not agree that this situation is analogous because **screening** to **identify** the desired hybridoma necessarily assumes that a percentage of the pool produces the monoclonal antibody sought. This is not the case for the production of transgenics. When a founder is identified, it may or may not have the desired phenotype (i.e.

maturity onset obesity). If it does not have the desired phenotype, a new experiment with new transgene constructs must be undertaken. The results of these further experiments are equally unpredictable. In other words, in the monoclonal antibody situation, the probability of the desired hybridoma being present is 100%, even if only 2.3% of the hybridomas in the pool are the correct one; then it is just a matter of identifying and isolating the correct one. In the case of transgenics, the "correct" one, i.e. the one with the desired phenotype may not be present at all. Further, monoclonal antibody technology involves performing one method repetitively (producing the hybridomas and then screening the products for the correct clone). This is not the case with transgenics, where various transgene constructs must be designed and tested out one by one, without specific guidance for the direction in which experimentation should proceed. There is no predictability for generating a pool of transgenics where at least one animal in the pool is the one sought after, the way there is in hybridoma screening. Appellants state that "[i]t is common, and considered acceptable, that several attempts may be required to produce a transgenic rodent expressing a desired transgene." As discussed above, **expression** is **not sufficient** to enable the claimed invention.

Appellants argue that the burden of proof was shifted to the examiner, who has provided no additional evidence in response to that of the Appellants. On the contrary, Appellants have cited only one example where a transgenic experiment produced the same phenotype in both rats and mice. The art cited was **post-filing** art, and therefore does not point to predictability in the art at the time of the invention. The Examiner, on the other hand,

has come up with two examples showing that rats and mice harboring identical transgenes exhibit widely varying phenotypes. Furthermore, Wall (1996) discusses the unpredictability in the art with respect to extrapolating from one species to another (p. 62, paragraph 1). The evidence that the Examiner has cited is representative of the state of the art **at the time of filing**, and clearly establishes unpredictability in the art.

It is noted that the filing date indicated on the front page of Appellants' Appeal Brief is incorrect. The actual filing date is November 6, 1997.

It is again noted that Appellants' arguments and all references cited by Appellants are limited to the **rat**. However, the claims are directed to all rodents. There are **4,000 species** of rodents. The specification is not enabling over the full scope of **all rodents**.

Appellants state on page 15 of the Appeal Brief "[n]ot only has the examiner failed to provide any response to the evidence that appellants have provided, other than to reiterate the rejections, but the office action mailed February 1, 2000 appears to be a word processed copy of the rejection. This is clearly improper. The examiner must do more than reiterate the same rejections in view of the appellants response." Appellants appear to be ignoring the four pages of response to Applicants' arguments appearing on pages 6-9 of the final rejection. Each argument profferred by Applicant was addressed in its entirety. There is nothing improper about the final rejection of 2/1/00.

For the above reasons, it is believed that the rejections should be sustained for Claims 1, 3-5, 10, and 12-14.

Claims 6 and 15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Respectfully submitted,

Anne-Marie Baker, Ph.D.
February 23, 2001

Deborah Clark
DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

DRC

Deborah Clark
conferee

Bruce Campell
conferee

Bruce Campell
conferee

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Patrea L. Pabst
ARNALL GOLDEN & GREGORY, LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450